REMARKS

Claims 24, 26-30 and 33-42 and 44-45 were previously pending, and are presented for examination.

35 U.S.C. § 103(a)

All pending claims are rejected under 35 U.S.C. § 103(a) as obvious over Bennett et al. (WO 92/03139) and Bennett et al. (US 6,077,833) in view of Wright et al. (US 5,795,876), Cook et al. (US 6,440,943) and Wollyniec et al. (Am. J. Resp. Cell & Molec. Biol., 18:777-785 (1998)), further in view of Wang et al. (US 6,403,566).

In their previous response, Applicants argued that none of the cited references disclose administration of any oligonucleotide compounds into the lung, including ICAM-1 oligonucleotides, and that none of the cited references disclose that ICAM-1 oligonucleotides reduce eosinophil recruitment into the lung, particularly when administered via the lung. Applicants also noted that there was no support in the cited references for the Office's assertion that Bennett '833 discloses that antisense of SEQ ID NO: 22 reduces eosinophilia in a human.

In response to Applicants' arguments, the Office withdrew its previous rejection, and entered a new rejection which is nearly identical to the previously pending rejection, with the exception of the newly cited Wright reference. Applicants acknowledge that the assertion that Bennett '833 discloses reduction of eosinophilia has been withdrawn by the Office, and that the Office acknowledges that Bennett and Bennett do not disclose "the administration of therapeutic agents to inhibit eosinophil infiltration in the lungs." *Office Action* at page 4.

To overcome the deficiencies in Bennett and Bennett, the Office asserts that the newly cited Wright reference teaches "the administration of antisense in vivo to inhibit eosinophil infiltration and accumulation in the lungs (see esp. paragraphs 173-175, example 19)." *Id.* Based on this disclosure, and the previously cited references, the Office concludes that the claimed invention would have been obvious to one of skill in the art, and that one of skill in the art "would have reasonably expected that SEQ ID NO. 22, ... would provide for the treatment effects claimed, including reducing inflammation and reducing eosinophilia, relying on the prior art teachings of Wright, Bennett, Bennett, Cook, Wang and Wollyniec." *Id.* at pages 5-6.. Applicants respectfully traverse.

To establish a *prima facie* case of obviousness, the Office must establish that there is a reasonable expectation of success in practicing the claimed invention. In the instant case, there must be a reasonable expectation of success in being able to administer the claimed compounds via the lung such that ICAM-1 expression is inhibited and eosinophil recruitment into the lung is reduced. For the reasons of record in Applicants' previous response, which are included by reference in the instant response, and for the reasons below, Applicants submit that the Office has not established a *prima facie* case of obviousness.

Applicants submit that the newly cited Wright reference does not overcome the deficiencies in the Office's argument which were identified in Applicants' previous response. In particular, the cited references do not provide a reasonable expectation that oligonucleotide compounds targeting ICAM-1 can be successfully administered via the lung, or that ICAM-1 oligonucleotide compounds so administered will reduce eosinophil recruitment into the lung.

The Office asserts that "Wright et al (USPN 5,795,876) teach the administration of antisense in vivo to inhibit eosinophil infiltration and accumulation in the lungs (see esp. paragraphs 173-175, example 19)." *Id.* at 4. Applicants cannot find support in Wright for this assertion. As far as Applicants are aware, Wright does not mention antisense in Example 19 or anywhere else (Applicants note that Wright does not contain paragraph numbers). Applicants invite the Office to point to disclosure of antisense in Wright. In addition, Wright only mentions eosinophilia twice, in the paragraph spanning columns 19 and 20. Wright states:

> In vivo activity of these compounds [which do not include antisense] can also be assessed in other models of inflammation predicted to involve elevated VCAM-1 levels. One such model for respiratory diseases, such as asthma, is an ovalbumin-sensitized model. This model of pulmonary inflammation is IgE mediated and involves eosinophillia (as does the asthmatic human). The bronchial alveolar lavage (BAL) fluid obtained from experimental animals can be assessed for a number of parameters, including soluble adhesion molecule expression and leukocyte accumulation. Adhesion molecule expression can be assessed by immunohistochemistry within the tissues, especially the lung, of experimental animals. The effect of the claimed compounds, such as MDL 29,353, should be to suppress the upregulation of VCAM-1 expression and inhibit eosinophil accumulation in the BAL fluid. *Wright* at col. 19, line 57 through col. 20, line 5 (emphasis added, citation omitted).

This passage makes no mention of antisense or ICAM-1, and it only mentions VCAM-1's role in eosinophilia, not ICAM-1. In addition, the disclosed compounds are administered in food, not

into the lung. *Id.* at col. 19, lines 40-43. Thus, contrary to the Office's assertion, Wright does not "teach the administration of antisense in vivo to inhibit eosinophil infiltration and accumulation in the lungs."

In view of the above, Applicants maintain that none of the cited references provide a reasonable expectation that oligonucleotide compounds generally, or ICAM-1 compounds specifically, can be successfully administered via the lung, or that inhibition of ICAM-1 will reduce eosinophil infiltration into the lung.

As noted in the previous response, the only disclosure regarding eosinophils and ICAM-1 in Cook is the following sentence: "Moreover, intraperitoneal administration of a monoclonal antibody to ICAM-1 decreases ovalbumin-induced eosinophil infiltration into skin in mice." *Cook* at col. 30, line 33-36 (emphasis added, citations omitted). There are numerous differences between the claimed method and the disclosure in Cook which makes this disclosure irrelevant to providing a reasonable expectation of successfully practicing the claimed methods: the disclosure relates to ICAM-1 antibodies, not oligonucleotide compounds; the disclosure relates to i.p. administration of the antibodies, not administration into the lung; and the result relates to eosinophil infiltration into the skin, not the lung. Thus Cook does not provide a basis for concluding there is a reasonable expectation of success in practicing the claimed methods.

The Office asserts that Wolyniec "teach reduced inflammation and eosinophilia in ICAM-1 deficient mice." *Office Action* at page 4-5 (citations omitted). According to the reference, ICAM-1 knockout mice were tested in an animal model of asthma. However, the authors urge caution in drawing conclusions based on the experiments:

> [L]imitations in forming conclusions from gene-knockout mice should be considered. As an example, Kumasaka and colleagues have described a role for ICAM-1 in a model of endotoxin-induced lung neutrophilia. Antisense oligonucleotides and monoclonal antibodies to ICAM-1 provided inhibition of the lung neutrophilia, whereas the ICAM-1 gene knockout was comparable to the wild type. *Wolyniec* at page 778, left col., first full paragraph (emphasis added, citation omitted).

It is clear from this paragraph that antisense, antibody, and gene knockout experimental results for ICAM-1 are not necessarily predictive of each other.

In addition, Applicants note that knockout mice differ from mice administer antisense in an important way. Knockout mice are born ICAM-1 deficient, and never expressed ICAM-1.

Thus their development of airway hyperresponsiveness following ovalbumin (OVA) was affected by the absence of ICAM-1 during the entire exposure period. In contrast, in the instant case administration of the ICAM-1 antisense began on day 15, after the animals were initially exposed to OVA on days 0 and 14. Thus, because knockout animals did not express ICAM-1 during the initial OVA exposure (sensitization stage) as well as during the challenge stage, knockouts are not equivalent to experiments in which antisense was administered only during the challenge stage. As patients with inflammatory diseases such as asthma presumably express ICAM-1 throughout their lives, the knockout experiments are less likely to reflect therapeutic efficacy than antisense experiments.

For at least these reasons, the ICAM-1 antibody and gene knockout evidence in Cook and Wolyniec does not provide a reasonable basis to believe that oligonucleotide compounds targeting ICAM-1 administered via the lung will reduce eosinophil infiltration into the lung.

This assertion is supported by the additional example discussed in the previous response, incorporated herein, where the successful inhibition of a target *in vivo* by a non-oligonucleotide compound was not predictive of the *in vivo* activity of oligonucleotide compounds to the same target, even where the oligonucleotide compounds worked *in vitro*. *See Monia Declaration and Previous Response* at pages 8-9. These results further support the cautionary note made in the Wolyniec reference – antisense, antibody, gene knockout and small molecule inhibitor studies are not interchangeable. The knowledge that a particular target is involved in eosinophilia, and that inhibiting the target using non-oligonucleotide means reduces eosinophilia, is not sufficient to conclude that oligonucleotide compounds to the same target administered via the lung will have the same effect. Given this evidence, Applicants submit that one of skill in the art would not have a reasonable likelihood of success at practicing the claimed methods based on the references cited by the Office in the instant case.

In view of the lack of a reasonable expectation of success, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness. For at least this reason, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 103(a) as obvious over the cited references.

No Disclaimers or Disavowals

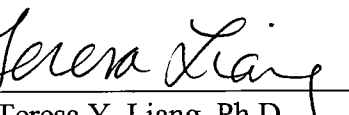
Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

Applicants submit that the present application is in condition for allowance and respectfully requests an action to that effect. If any issues remain, the Examiner is invited to contact Applicants' counsel at the number provided below in order to resolve such issues promptly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 50-0252 referencing case number ISPH-0852USA.

Respectfully submitted,

Dated: December 27, 2010

By: 

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